CLINICAL TRIAL DESIGN IN DIABETIC FOOT INFECTIONS

This FDA briefing document serves as a synopsis for the discussion of issues in the design of clinical trials for the treatment of diabetic foot infections (DFIs). Historically, clinical trials evaluate the efficacy and safety of drug in subjects with DFIs as a subset of patients within a larger clinical trial population of patients with complicated skin and skin structure infections (cSSSIs). However, in the review of clinical trials for cSSSIs there are several issues relating to the subset of patients with DFIs that warrant further discussion and clarification. The public health impact of DFIs is significant, considering the estimated 17.1 million diabetics in the United States at present[1]. Diabetics have an increased risk of lower extremity cutaneous ulcers due to underlying peripheral neuropathy and vascular disease, and a high rate of lower extremity amputations. Thus, there is clearly the need to encourage drug development for DFIs utilizing a standardized clinical trial design to assess the efficacy and safety of such agents.

Drug sponsors have made several recent requests to the FDA regarding the design of clinical trials of drugs for DFIs. However, the review of such trials is complex since the trials generally lack standardized methods for: 1) defining a "diabetic foot infection", 2) obtaining microbiological specimens and determining microbiological outcomes, 3) radiological assessment for excluding bone and joint involvement, and 4) determining clinical outcomes in DFIs.

Currently, there are three drugs approved for the treatment of diabetic foot infections as part of the cSSSI indication: piperacillin/tazobactam (Zosyn™), trovafloxacin (Trovan™), and linezolid (Zyvox™). There are no agents approved specifically for the treatment of osteomyelitis associated with an overlying diabetic foot infection.

The issues for discussion before the Advisory Committee will include:

1. How does one define a "diabetic foot infection"? Please include in your discussions the considerations of patients with cellulitis without breaks in the skin versus patients with pre-existing breaks in the skin.
2. In patients with a pre-existing skin ulcer, how does one define infected versus non-infected ulcers?
3. What is the most accurate way to obtain microbiologic information in patients with diabetic foot infections?
4. What are the considerations for clinical trials for ruling out osteomyelitis in patients in trials of diabetic foot infections? Please discuss how to determine drug efficacy for the diabetic foot infection in the setting of osteomyelitis and whether such patients should be considered clinical cures or failures.
5. How does one define clinical success or failure patients in a clinical trial of diabetic foot infections?

[1] National Diabetes Statistics. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#7. Accessed September 22, 2003.